

WIDN.SLR 06/27/05 397504.doc E-231-1998/0-US-04
PATENT

Attorney Reference Number 4239-67517-01
Application Number 10/731,988

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Suresh K. Arya, Ph.D.

Application No. 10/731,988

Filed: December 9, 2003

Confirmation No. 9402

For: LENTIVIRUS VECTOR SYSTEM

Examiner: Myron G. Hill

Art Unit: 1648

Attorney Reference No. 4239-67517-01

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COMMISSIONER FOR PATENTS
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DECLARATION UNDER 37 C.F.R. § 1.132

1. I, Tal Kafri, M.D. Ph.D., am an expert in the field of lentivirus vectors for gene therapy, such as HIV-based vectors. I hold an M.D. Ph.D. from Hebrew University, Jerusalem. I am currently an Assistant Professor in the Department of Genetics and Molecular Biology at the University of North Carolina at Chapel Hill. I presently have over 20 publications in the field of lentivirus vectors. A copy of my Curriculum Vitae is attached (Exhibit A).

2. It is my understanding that some of the claims of the above-referenced patent application are directed to an HIV-2 packaging cassette that includes a functional 5' splice donor site, and functionally deleted upstream and downstream packaging signal sequences, thereby reducing packaging of progeny viral RNA.

3. It is also my understanding that some of the claims of the above-referenced patent application were rejected on the ground that it would be difficult to determine how many nucleotides, and which particular nucleotides, within the upstream and downstream packaging signal sequences could be deleted (or otherwise altered) to achieve the desired effect of reducing packing of viral RNA.

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Application Number 10/731,988

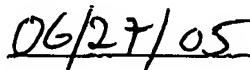
4. It is routine and straight-forward in the field of lentiviral vectors to functionally delete one or more specific nucleotides from upstream and downstream packaging signals in an HIV vector, for example in singles, pairs, triples, or greater numbers of nucleotides. For example, mutations, insertions, or deletions can be made to nucleotides in upstream and downstream packaging signals in an HIV vector using standard recombinant nucleic acid technologies.

5. It is also routine in the field of lentiviral vectors to identify the minimum number of nucleotides that can be deleted or otherwise altered in the upstream and downstream packaging signal to achieve an HIV packaging defective vector. For example, progressive deletions in the upstream and downstream packaging signal sequences can be made, for example in combinations of single nucleotides, pairs of nucleotides, or triplets of nucleotides, or larger regions. The resulting HIV vectors are then tested for their ability to be packaged using standard methods, for example by measuring the amount of particle-associated viral RNA in the supernatant of a cell culture infected with the modified vectors. This permits identification of the minimal deletion needed in the upstream and downstream packaging signal to achieve an HIV packaging defective vector.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Tal Kafri, M.D. Ph.D.



Date

TAL KAFRI

CURRICULUM VITAE

Personal:

Name: Tal Kafri
Nationality: USA & Israel
Social Security No. 604-74-3403
Home Address: 208 Blueridge Rd, Carrboro NC 27510
Phone: W- 919 843 7635 H- 919 942 1108
Date of Birth: 11/16/59, Israel
Marital Status: Married; two children

Education:

1981-1989 Medical studies, Hebrew University at Jerusalem Israel
1984 B.Sc. in Medical Sciences (with distinction)
1984-1985 Research project-Dept. of Cellular Biochemistry Hebrew University at Jerusalem Israel
1989 M.D. granted
1989 Certified Advanced Combative Trauma Life Support (ACTLS)
1989-1990 Internship, Hadassah University Hospital at Jerusalem Israel
1990-1994 Ph.D. (Thesis: "Formation of DNA methylation patterns in imprinted and non-imprinted genes", under the supervision of Prof. A. Razin, Dept. of Cellular Biochemistry Hebrew University at Jerusalem Israel
1994 Ph.D. granted (Summa Cum Laude)
1994-1999 Post doctoral fellow Salk Institute La-Jolla CA USA

Fellowships:

1994-1996 EMBO, postdoctoral fellowship.,
1996-1999 Cystic Fibrosis, Postdoctoral fellowship.,

Awards:

2000-2003 National Hemophilia Foundation Career Development Award.

Prizes :

1982 Dean's List
1984 Foulkes Foundation Scholarship
1990 Faculty award for distinguished M.D. thesis
1994 Faculty award for distinguished Ph.D. thesis



Professional experience:

- | | |
|--------------|--|
| 1991-1993 | Physician, Jerusalem Mobile Intensive Care Unit |
| 1994-1999 | Research Associate, Laboratory of Genetics, The Salk Institute, La Jolla, CA |
| 1999-present | Assistant Professor Microbiology and Immunology University of North Carolina Chapel Hill |
| 2005-present | Interim Director of Gene Therapy Center, University of North Carolina at Chapel Hill USA (During sabbatical of center director, Dr. Jude Samulski) |

Professional Activities:

- Member, American Society of Gene Therapy, 1996-Present
Member, American Society of Neuroscience, 2004-Present

Professional Service

International level

Reviewer

- 2005 RNA viral vectors abstract reviewer at the 8th annual meeting of the American Society of Gene Therapy.

Coordinator

- 2005 Educational program entitled “regulation of Gene Expression”, at 8th Annual Meeting of the American Society of Gene Therapy. St. Louis, Missouri.

Chair Session

- 2005 Educational program entitled “regulation of Gene Expression”, at 8th Annual Meeting of the American Society of Gene Therapy. St. Louis, Missouri.

- 2005 RNA viral vectors at the 8th annual meeting of the American Society of Gene Therapy.

Invited speaker

- 2000 11th Institute of Molecular Pathology Spring Conference. Vienna, Austria.

- 2001 4th Annual Meeting of the American Society of Gene Therapy. Seattle, WA.

- 3rd International Symposium on Transplantation & Gene Therapy, Idar-Oberstein, Germany.

- Glaxo Welcome Adrenoleukodystrophy Gene Therapy Meeting. Philadelphia, PA.

- 2002 5th Annual National Hemophilia Foundation Workshop on Gene Therapy for Hemophilia Philadelphia, PA.

- 2003 6th Annual Meeting of the American Society of Gene Therapy. Washington, DC.

2005 8th Annual Meeting of the American Society of Gene Therapy. St. Louis, Missouri.

National level

Invited speaker in meetings

2002 Tranzyme, Inc. Lentiviral Vector Packaging Cell line Seminar. Birmingham, Al.

2004 Clontech, Inc. Gene delivery Seminar. Palo-Alto, CA.

Study Sections and Reviews

2002 Study section NIDDK; Special Emphasis Panel for RFA-DK-02-020 (Ad hoc member).

2004 Study section Developmental Therapeutics. For RFA-CA-01-040 (Ad hoc member).

Reviewer of a pilot and feasibility proposal to the Molecular Core Therapy Center at the University of Washington School of Medicine at Seattle WA.

2002-2005 Extramural Advisory Committee for NIH program project grant, "Gene Therapy for Metabolic Disorders" (PO1-HD32652). Department of Pediatrics and Institute of Human Genetics, University of Minnesota

2005 Study section NHLBI. For RFA-HL-04-017; "Specialized Centers For Cell-Based Therapy.

Editorial Board

2001-Present Current HIV Research

Department level

2003 Department of microbiology and immunology; Admission of special student committee ad hoc committee

2004-present Member Gene Therapy Center faculty position search committee.

Patents

1. Patent: *Retroviral Packaging Cell Line*

Inventors: Inder Verma, Tal Kafri, Frederic Bushman, Mark Hansen

Applications: Gene Therapy

Patent Status: U.S. Patent Number 6,218,181 issued April 17, 2001; PCT/US99/05982

Owner: Salk Institute

2. Patent: *Assay for Integration Inhibitors Using Pre-Integration Complexes*

Inventors: Frederic Bushman, Tal Kafri, Mark Hansen

Applications: Infection, HIV, Drug Discovery A screen for viral integrase inhibitors

Patent Status: U.S. Application Published as US2001/0009772, PCT/US99/05982
Owner: Salk Institute

Patents Pending

1. Patent: *A Single LTR Lentivirus Vector*
Inventors: Tal Kafri, Hong ma
Applications: Functional Genomics
Patent Status: Application Number 10/721,563; Filed November 25, 2003
Owner: Tal Kafri, Hong Ma

Bibliography:

Peer-Reviewed Publications before arrival at UNC (in reverse chronological order)

Somia, NV., Kafri, T., Verma, IM. Piecing together more efficient gene expression. *Nat Biotechnol* 17:241-245, 1999.

Leibowitz, G., Beattie, GM., Kafri, T., Cirulli, V., Lopez, AD., Hayek, A., Levine, F. Gene transfer to human pancreatic endocrine cells using viral vectors. *Diabetes* 48:745-753, 1999.

Hansen, M.S., Smith, G.J., Kafri, T., Molteni, V., Siegel, J.S., Bushman, FD. Integration complexes derived from HIV vectors for rapid assays *in vitro*. *Nat Biotechnol* 17:578-582, 1999.

Kafri, T., Von-Praag, H., Ouyang, L., Gage, F., Verma, I.M. High titer lentiviral vector A packaging cell line for lentivirus vectors. *J Virol* 73:576-584, 1999.

Gallichan, W.S., Kafri, T., Krahl, T., Verma, I.M., Sarvetnick, N. Lentivirus-mediated transduction of islet grafts with interleukin 4 results in sustained gene expression and protection from insulitis. *Hum Gen Ther* 9:2717-2726, 1998.

Kafri, T., Morgan, D., Troy Krahl., Sarvetnick, N., Sherman, L., Verma, I.M. Cellular immune response to inactive recombinant adenoviruses implications: for gene therapy. *Proc Natl Acad Sci USA* 95:11377-11382. 1998.

Blomer, U., Kafri, T., Randolph-Moore, L., Verma, I.M. Gage, F.H. Bcl-xL protects adult septal cholinergic neurons from axotomized cell death. *Proc Natl Acad Sci USA* 95:2603-2608, 1998

Kafri, T., Blomer, U., Peterson, D., Gage, F., Verma, I. M. Sustained expression of genes delivered directly into liver and muscle by lentiviral vectors. *Nat Genetics* 17:314-317, 1997.

Blomer, U., Naldini, I., Kafri, T., Trono, D., Verma, I.M., Gage, F. Highly efficient and sustained gene transfer in adult neurons with a lentivirus vector. *J Virol* 71:6641-6649, 1997.

Van Antwerp, D., Martin, S., Kafri, T., Green, G. and Verma, I. NF- κ B activation by TNF α suppresses signals for apoptosis: evidence for a negative feedback mechanism. *Science* 274:787-789, 1996.

Razin, A. and Kafri, T. DNA methylation from embryo to adult. *Prog Nucleic Acid Res Molec Bio* 48:53-81, 1994.

Ariel, M., Selig, S., Brandeis, M., Kitsberg, D., Kafri, T., Weiss, A., Keshet, I., Razin, A. and Cedar, H. Cold Spring Harbor Symposia on Quantitative Biology LVIII, 307-313, 1993.

Kafri, T., Xiaohong, G. and Razin, A. Mechanistic aspects of genome-wide demethylation in the preimplantation mouse embryo . *Proc Natl Acad Sci (USA)* 90:10558-10562, 1993.

Brandeis, M., Kafri, T., Ariel, M., Chaillet, R., McCarrey, J., Razin, A. and Cedar, H. The ontogeny of allele-specific methylation associated with imprinted genes in the mouse . *EMBO J*, 12:3669-3677, 1993.

Kafri, T., Hershko, A. Razin, A. Probing CpG methylation at CACGTG with BbrPI restriction enzyme. *Nucleic Acids Research* 21:2950, 1993.

Stoger, R., Kubica, P., Lin, C.G. Kafri, T., Razin, A., Cedar, H. and Barlow, D.P. Maternal-specific methylation of the imprinted mouse Igf2r locus identifies the expressed locus as carrying the imprinted signal. *Cell* 73:61-71, 1993.

Kafri, T., Ariel, M., Brandeis, M., Shemer, R., Lomer, U., McCarrey, J., Cedar, H. and Razin, A. Developmental pattern of gene-specific DNA methylation in the mouse embryo and germ line. *Genes Development* 6:705-714, 1992.

Shemer, R., Kafri, T., O'Connell, A., Eisenberg, S., Breslow, J.L. and Razin, A. Methylation changes in the apo A1 gene during embryonic development of the mouse . *Proc. Nat. Acad. Sci. (USA)* 88:10300-10304, 1991.

Razin, A., Levine, A., Kafri, T., Agostini, S., Gomi, T. and Cantoni, G.L. Relationship between transient DNA hypomethylation and differentiation. *Proc Nat Acad Sci (USA)* 85:9003-9006, 1988.

Razin, A., Levine, A., Kafri, T., Agostini, S. and Cantoni, G.L. DNA hypomethylation and differentiation of Friend erythroleukemia cells. *Gene* 74:139-141, 1988.

Razin, A., Szyf, M., Kafri, T., Roll, M., Giloh, H., Scarpa, S., Carotti, D. and Cantoni, G.L. Replacement of 5-methylcytosine by cytosinem - A possible mechanism for transient demethylation during differentiation. *Proc Nat Acad Sci (USA)* 83:2827-2831, 1986.

Razin, A., Feldmesser, E., Kafri, T. and, M. Szyf, Cell-specific DNA methylation patterns: formation and a nucleosome locking model for their function. In "Biochemistry and Biology of DNA Methylation" (Cantoni, G.L. and Razin, A., eds.), Alan R. Liss Inc/New York, pp. 239-253, 1985.

Peer reviewed articles since arrival at UNC (in reverse chronological order)

Bahi, A., Boyer, F., Kafri, T., Dreyer, J.L. In vivo gene delivery of urokinase-type plasminogen with regulatable lentivirus induces behavioural changes in chronic cocaine administration. *Eur J Neurosci* 20:3473-88, 2004

The development of the inducible lentiviral vectors for this study was done in Dr. Kafri's lab.

Haack, K., Adam, S.C., Ma, H., Israeli, D., Ho, S.N., McCown, T.J. Kafri, T. Transactivator and structurally optimized Inducible lentiviral vectors. *Mol Therapy* 10:585-96, 2004

All the studies were carried in Dr. Kafri's lab. Dr. Kafri edited and revised the manuscript and he is the corresponding author.

Logan, A.C., Haas, D.L., Kafri, T., Kohn, D.B. Integrated self-inactivating lentiviral vectors produce full-length genome transcripts competent for encapsidation and integration. *J virol* 8421-8431, 2004.

The laboratory of Dr. Kafri established the novel HIV-1 vector packaging cell line, which was essential for the study.

Ma, H., Kafri, T. A single LTR HIV-1 vector optimized for functional genomics applications. *Mol Therapy* 10:139-149, 2004

All the studies were carried in Dr. Kafri's lab. Dr. Kafri wrote the manuscript and he is the corresponding author.

Bahi, A., Bover, F., Kafri, T., Dreyer, J.L. CD81-induced behavioural changes during chronic cocaine administration: *in vivo* gene delivery with lentivirus. *Eur J Neurosci* 6: 1621-33, 2004.

The development of the inducible lentiviral vectors for this study was done in Dr. Kafri's lab.

Cockrell, A.S., Kafri, T. HIV-1 vectors: fulfillment of expectations, further advancement, and still a way to go. *Curr HIV research* 4:419-39, 2004. *Edited and revised by Dr. Kafri who is the corresponding author.*

Hershko, A.Y., Kafri, T., Fainsod, A., Razin, A. Methylation of HoxA5 and HoxB5 and its relevance to expression during mouse development. *Gene* 302:65-72, 2003.

A major part of the study was done by Dr. Kafri.

Vacek, M.M., Ma, H., Gemignani, F., Lacerra, G., Kafri, T., Kole, R. High-level expression of hemoglobin A in human thalassemic erythroid progenitor cells following lentiviral vector delivery of an antisense siRNA. *Blood* 101:104-111, 2003.

The design, construction, and production of the siRNA vectors and the transduction of the human bone marrow cells was done in Dr. Kafri's lab, who is also a corresponding author.

Pan, D., Gunther, R., Duan, W., Wendell, S., Kaemmerer, W., Kafri, T., Verma, I.M., Whitley, C.B. Biodistribution and toxicity studies of VSVG-pseudotyped lentiviral vector after intravenous administration in mice with the observation of *in vivo* transduction of bone marrow. *Mol Ther* 6:19-29, 2002.

The packaging cell line, which was used in the study, was generated in Dr Kafri's lab (part of aim 1 in ROI).

Xu, K., Ma, H., McCown, T.J., Verma, I., Kafri, T. Generation of a stable cell line producing high-titer self-inactivating lentiviral vectors. *Mol Therapy* 3:97-104, 2001.

All the studies were carried in the Kafri lab. Dr. Kafri wrote the manuscript and he is the corresponding author.

Kafri, T., Von-praag, H., Oyang, L., Gage, F., Verma, I.M. *In vivo* regulation of transgenes delivered by lentiviral vectors. *Mol Therapy* 1:516-521, 2000.

Dr. Kafri perform most of the work and wrote the manuscript.

Published peer reviewed poster abstracts

Cockrell, A., Ma, H., McCown, T., Kluckman, K., Thresher, R., Kafri, T. A HIV-1 based cross-packaging system for FIV vectors. 8th annual ASGT meeting. 2005

Ma, H., Cockrell, A., Bash, R., Terry, VanDyke., Kafri, T. A Rev/RRE dependent packaging system for MLV based vectors raises biosafety concerns. 8th ASGT meeting. 2005

Cockrell, A., Fu,K., Ma, H., McCown, T., Kafri, T. Closing-in the titer gap between transient transfection and packaging cell lines. 7th ASGT meeting. *Mol Therapy* 9:S28. 2004

McCown, T., Ma, H., Haack, K., Heise, M., Kafri, T. Hit them on their way: potential targeting of neuronal progenitors with lentiviral vectors. 6th annual ASGT meeting. *Mol Therapy* 7:S152. 2003 Oral presentation

Ma, H., Kafri, T. When a self inactivating (SIN) vector is not a sin: characterization of episomal HIV-1 vectors. 6th annual ASGT meeting. *Mol Therapy* 7:S3. 2003 Oral presentation

Ma, H., Kafri, T. A single copy LTR lentivirus vector constructallows efficient vector production. 5th annual ASGT meeting. *Mol Therapy* 5:S305. 2002

Fu, K., Ma, H., McCown, T., Kafri, T. A split HIV-1 Gag/Pol packaging cell line. 5th annual ASGT meeting. *Mol Therapy* 5:S305, 2002

Haack, K., Ma, H., McCown, T., Kafri, T. Characterization of regulated transgene expression from inducible lentivirus vectors in primary cells in culture and in vivo. 5th annual ASGT meeting, *Mol Therapy* 5:S33, 2002

Xu, K., Ma, H., McCown, T., Verma, I., Kafri, T. Generation of a stable cell line producing high titer self-inactivating lentiviral vectors. 4th annual ASGT meeting. *Mol Therapy* 3:S325, 2001

Haack, K., Kafri, T. Development of second generation inducible lentiviral vectors. 4th Annual ASGT meeting. *Mol Therapy* 3:S2, 2001 Oral presentation

Non-peer reviewed publications

Book Chapters

Kafri, T. Gene delivery by lentivirus vectors an overview. *Methods Mol Biol* 246:367-90, 2004.

Commentary

Kafri, T. Air-conditioning for regulated transgene expression. *Gene Therapy*. Online December 23, 2004.

Review articles

Kafri, T. Lentivirus vectors: difficulties and hopes before clinical trials. *Curr Opin Mol Therapy* 3:316-326, 2001.

Teaching Experience:

International level

- 2005 **Coordinator** of an educational program entitled : Regulation of Transgene Expression at the American Society of Gene Therapy 8th Annual Meeting. The duties include program planning and invitation of international level speakers in the field of gene regulation.
- 2005 **Speaker and Chair** at the educational session at the American Society of Gene Therapy 8th Annual Meeting.

University level

Graduate students program

Virology Seminar/Tutorial (MCRO 211). Spring 2000, 2001 (8h of formal lecture and **course director**), Virology (MCRO130). Spring 2000, 2001 (4h of formal lectures).

Virology (MCRO130). Spring 2002-present (12h of formal lectures and course **co-director**, was present at all 60h of formal lectures).

Medicine for the 21st Century (PHCO221). Fall 2003, 2004 (2h formal lectures).

The UNC Gene Therapy Center seminar series. Spring/Fall 2003-present (**director**, invited and coordinated outside campus speakers)

Graduate student thesis Supervision

2004-present Matthew Bayer Program: Curriculum of genetics

Graduate student rotation Supervision

2004 Mike Washburn

Graduate rotation project reviewer

2004 Thomer Aaron.

Oral examination of graduate students in the Dept of Microbiology and Immunology

2004 Common reviewer Students: Reed Shabman, Bernardo Mainou, Carlos Gonzalez, Milloni Patel, Catherine Siler.

Graduate Thesis Committee

2001-2004	Marla Vacek	Program: Curriculum of Genetics
2002-Present	Joshua Grieger	Program: Curriculum of Genetics
2004-present	Devon Gregory	Program: Curriculum of Genetics
2004-Present	Stacey Foti	Program: Curriculum of Neurobiology

Pre-Graduate Supervision

Summer Pre-Graduate Experience Program (SPGRE),

2002 Student: Kendrix Evans

The SPGRE program is an effort to address the shortage of Ph.D. recipients from different minority groups. The program is aimed at junior students who are offered the opportunity to work for two months on a research project under the direction of a UNC-CH faculty member. During the two months that Mr Evans has spent in my laboratory, he expanded his knowledge in virology and basic molecular biology. In addition, he significantly improved his scientific writing.

Research Support

Past research support

“Correction of hemophilia with lentiviral vectors”

Career Development Award (T. Kafri, PI)
Foundation

Role: Principle Investigator

These studies will determine the ability of lentiviral vectors carrying the canine factor IX cDNA to correct factor IX deficiency in canine and murine animal models.

Agency: National Hemophilia

Dates: 07/01/00 – 06/30/03

Current research support

Lentiviral vector based gene therapy for liver diseases””

Type: 1 RO1 DK 58702-05 (T. Kafri, PI)

Role: Principle Investigator

The overall goal of this study is to validate our hypotheses that lentiviral vectors can serve as an efficient and safe platform for therapeutic gene delivery to liver tissue.

Direct cost: \$219,000 Effort: 35%

Agency: NIDDK

Dates: 12/01/2000 – 11/30/05

“Gene Therapy of Pulmonary and Hematologic Disorders”

Type: 1 PO1 HL66973-01A1 (R. Jude Samulski, PI)

Role: Co-Investigator

The goal of this project is to advance lentiviral gene delivery systems to a point where they can serve as a safe and efficient therapeutic delivery systems for human clinical trials.

Wrote and run 2 out of 3 aims. In charge of 60% of the direct costs.

Direct costs: \$183,236 Effort: 23%

Agency: NIHHL

Dates: 09/30/99 – 07/31/06

“Molecular Therapy Core Center”

Type: 1 PO1 DK065988-01 (R. Boucher, PI)

Role: PI of pilot feasibility project

Agency: NIDDK

Dates: 12/01/03 – 09/29/08

The overall goal of this pilot feasibility project is to develop a novel simple-retroviral vector system as a means to generate transgenic animals.

Wrote and run the pilot feasibility project.

Direct cost: \$46,000 Effort: 10%

“Transition to Androgen-Independence” (F. French, PI)

Type: 1 PO1 CA077739-06

Role: Co-Investigator

The goal of this study is to test the hypothesis that recurrent prostate cancer is dependent on the androgen receptor pathway.

Wrote and run a major part of 2 out of 3 aims.

Direct cost: To be determined Effort: 15%

Agency: NCI

Dates: 04/01/05 – 03/30/10

“Uniform Lenti Vector Packaging for Liver Gene Therapy”

Type: 1 RO1 HL081924-01

Agency: NHLBI

Role: PI

Dates: 07/01/2005-06/30/10

The goals of these studies are to determine the effects of vector specific (HIV-1, FIV) cis and trans elements on different vector characteristics including vector tumorigenicity, species-specific transduction blocks, and vector immunogenicity.

Status: Pending

Submitted grant applications

Renewal of RO1 March 1st 2005

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